REMARKS

Claims 1-36 are currently pending in the application. Applicants herein cancel claims 1-23 without prejudice. Claims 24-36 have been amended to incorporate the limitations of claims 1, 8, and 15. Claims 29, 33, and 36 are in independent form. No new matter has been added.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Kenneth I. Kohn, during a personal interview conducted on January 29, 2008, with the Examiner.

Claims 1-36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Masihi reference. Specifically, the Office Action holds that Masihi teaches that the immune system can be manipulated specifically by vaccination or nonspecifically by immunomodulation. Masihi further teaches that methyl inosine monophosphate (MIMP) is a thymomimetic immunomodulator capable of inducing the expression of T lymphocyte differentiation markers in human prothymocytes. The Office Action holds that MIMP has been shown to enhance mitogen-induced proliferation of lymphocytes, augment IgM plaque-forming cells, induce delayed-type hypersensitivity and normalize an impaired response to IL-2. The Office Action holds that Masihi does not explicitly teach compositions of MIMP and an active agent; however, Masihi teaches that non-antibiotic agents such as immunomodulators possessing antimicrobial activity offer a novel approach as an adjunct modality for the treatment of infectious and malignant conditions. The Office Action holds that the use of immunomodulators as adjuncts or complimentary components implicitly teaches combinations with conventional active agents such as vaccines. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the Masihi reference is respectfully requested.

"Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).

Masihi describes immunomodulation through compounds that are non-specific to infectious diseases and teaches that these compounds stimulate host defense mechanisms for various microbial infections. Masihi is not describing vaccines or adjuvants. Masihi merely describes previous work done by Applicants (Hadden, et al., Methyl inosine monophosphate: a potential immunotherapeutic for early human immunodeficiency virus (HIV) infection, Int J Immunopharmacol 1992; 14:555-63), namely, that MIMP is an immunomodulator and induces proliferation of lymphocytes. It was known that MIMP shows a response to PHA and induces T-cell markers in humans and mice. As stated in the background section of the present invention, MIMP enhances T-cell activity. There was no evidence at that time that MIMP or any other protected IMP could work effectively as an adjuvant to a vaccine, and thus, one would have no reason to use MIMP as an adjuvant as described by the Office Action. Just because one immunomodulatory compound has been used as an adjuvant does not mean that all immunomodulatory compounds can be used as adjuvants. See paragraph [0022] – "To date, however, the action of MIMP as a vaccine adjuvant has not been reported. Many adjuvants are antigen-specific and action to induce protection against one antigen does not necessarily predict protection against another." Also, see for example the journal abstracts included herein.

"Synthetic immune response modifiers, such as resiquimod, are Toll-like receptor 7 and 8 agonists that act as vaccine adjuvants, enhancing antigen-specific

antibody production and skewing immunity towards a Th1 response." Tomai, et al., Expert Rev Vaccines, 2007 Oct;6(5):835-47.

"For the induction of antigen-specific immune responses the use of adjuvants is critical." Partidos, et al., Vaccine, 2004 Jun 23;22(19):2385-90.

98% of known adjuvants are effective on B-cells. There are very few T-cell adjuvants. One such T-cell adjuvant is CpG, which is only effective in mice. It is generally known in the art that there is a need for T-cell adjuvants. Previous work with MIMP showed that it augmented B-cell dependent antibodies, and therefore, even though MIMP is known in other uses to stimulate a T-cell response, there is no reason to believe that MIMP *as an adjuvant* would stimulate a T-cell response. Because of the great need for T-cell adjuvants, if MIMP was known to stimulate a T-cell response as an adjuvant, such a finding would have been published. In other words, one would be able to detect a T-cell adjuvant response as in the amended claims. Instead, Applicants are the first to show such an effect with MIMP as an adjuvant. Support for the amendment to claims 24-26, 29-30, and 32-36 can be found in the Examples, and specifically paragraph [0117] in Example 2 and paragraph [0119] in Example 3.

One skilled in the art would not predict that MIMP would act successfully as an adjuvant and stimulate a T-cell response. It was unexpected that the protected IMP compounds of the present invention could be effectively used as adjuvants and stimulate a T-cell response instead of the predicted B-cell response. Applicants show that MIMP can be combined with active agents to be used as an adjuvant, such as with the flu vaccine and various other active agents, and achieve a T-cell response.

Since neither the cited reference alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: January 30, 2008

CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

Date of Electronic Filing: 2-7-08

I hereby certify that this correspondence is being electronically filed with the United States Patent & trademark Office on the above date.

Connie Herty

1: Expert Rev Vaccines. 2007 Oct;6(5):835-47.

Resiquimod and other immune response modifiers as vaccine adjuvants.

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Synthetic immune response modifiers, such as resiquimod, are Toll-like receptor 7 and 8 agonists that act as vaccine adjuvants, enhancing antigen-specific antibody production and skewing immunity towards a Th1 response. These compounds stimulate dendritic cells to secrete cytokines, upregulate costimulatory molecule expression and enhance antigen presentation to T cells. The compounds have demonstrated vaccine adjuvant properties in a number of animal models. The adjuvant effects can be enhanced by measures that allow the drug to stay localized with the vaccine without quickly entering the systemic circulation. Clinical studies demonstrate that topical application of resiquimod and analogs is safe and effective at activating the local immune response. For injection, resiquimod or a similar compound may need to be formulated to allow for local immune activation without induction of systemic cytokines.

PMID: 17931162 [PubMed - indexed for MEDLINE]

1: Vaccine. 2004 Jun 23;22(19):2385-90.

Modulation of immune responses with transcutaneously deliverable adjuvants.

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Transcutaneous immunisation is a novel vaccination strategy based on the application of antigen together with an adjuvant onto hydrated bare skin. This simple and non-invasive immunisation procedure elicits systemic and mucosal immune responses and therefore, it provides a viable and cost-effective strategy for disease prevention. For the induction of antigen-specific immune responses the use of adjuvants is critical. They potentiate and modulate the type of immune responses by stimulating the production of cytokines that drive the differentiation of T cells towards the Th1 or Th2-phenotype. These cells mediate protection against different infectious diseases and therefore, their selective induction is important for successful vaccination. In this review we give a brief overview of transcutaneously deliverable adjuvants and we discuss how they modulate immune responses to topically applied antigens.

PMID: 15193399 [PubMed - indexed for MEDLINE]